STUDIES ON THE MECHANISM OF THE MANNICH REACTION

BY

ELIZABETH JOYCE UNDERHILL

B.A., University of Toronto, 1946

A.M., University of Illinois, 1947

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
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R. UNIV. BIBLIOTHEEK LEIDEN

STUDIES ON THE MECHANISM OF THE MANNICH REACTION

Introduction

When a compound containing an active hydrogen atom is treated with formaldehyde and ammonia or a primary or secondary amine, the active hydrogen atom is replaced by an aminomethyl group.

$$-\overset{|}{\underset{|}{CH}} + CH_2O + HNR_2 \rightarrow -\overset{|}{\underset{|}{C}}-CH_2-NR_2 + H_2O$$

This reaction is commonly called the Mannich reaction (1), and it has been used widely in synthesis. Its mechanism, however, has not been elucidated. Many types of active methylene and methynyl compounds undergo the reaction, and it has been run in both acidic and basic media. It was the purpose of this investigation to determine the mechanism of the Mannich reaction with various model compounds.

Discussion Of Results

Kinetic studies have been carried out on the reactions of formaldehyde and dimethylamine with ethylmalonic acid (2) and with *p*-nitrophenylacetic acid (3). Mechanisms have been outlined for both reactions which are in agreement with the results obtained.

Ethylmalonic Acid —

1) In acid solution the Mannich reaction of ethylmalonic acid, formaldehyde, and dimethylamine, follows third order kinetics, first order in each of the components. A specific rate constant of 0.360 ± 0.033 liters^2/mole^{2}hr. was obtained for the reaction at $0.09 \pm 0.27°$, and at a *p*H of 4.20 ± 0.08.

2) The rate of reaction shows a critical dependence on *p*H. It passes through a maximum at about *p*H 3.8.

3) Under the conditions of the experiment no reaction between formaldehyde and ethylmalonic acid has been detected, and the Mannich reaction is non-reversible.

4) Smooth, third order curves are obtained for the reaction only if the amine and formaldehyde are mixed and allowed to stand together for twelve hours before adding the ethylmalonic acid, but if the formaldehyde and dimethylamine are replaced by dimethylaminomethanol, the reagents may all be mixed at once without affecting the kinetics in any way.

5) No reaction takes place in basic solution.

These facts are in agreement with an ionic mechanism for the reaction of methynyl compounds involving the acid catalyzed condensation of formaldehyde with the amine, followed by the addition of the resulting carbonium ion to the active hydrogen compound, probably in the enolic form. The rate determining step appears to be the removal of a proton from the final product.

p-NITROPHENYLACETIC ACID —

1) In acid, the Mannich reaction of *p*-nitrophenylacetic acid, formaldehyde, and dimethylamine, follows the third order kinetics, first order in each of the components, through about 55% of its course. A specific rate constant of 1.27 ± 0.12 liters^2/mole^{2}hr. was obtained for the reaction at $54.24 \pm 0.03°$, and at a *p*H of 4.20 ± 0.08.

2) The reaction rate increases as the ionic strength of the solution is increased by the addition of potassium chloride.

3) The rate of reaction shows a critical dependence on *p*H, passing through a maximum at about *p*H 5.3 and a minimum at about *p*H 6.4, and increasing rapidly as the *p*H increases beyond this.

4) Under the experimental conditions no reaction has been detected between formaldehyde and *p*-nitrophenylacetic acid, and the Mannich reaction is non-reversible.

5) Smooth, third order curves are obtained for the reaction when formaldehyde and dimethylamine are replaced by dimethylaminomethanol, and the specific rate constant is 1.34 liters^2/mole^{2}hr. under the experimental conditions indicated in 1) above.

6) The reaction in basic solution has not been investigated thoroughly.

The results obtained in acid solution are in agreement with an ionic mechanism for the reaction of methylene compounds. It consists in the acid catalyzed condensation of the amine with formaldehyde to form a carbonium ion, which adds to the enolic form of the active hydrogen compound. The effect of ionic strength upon the rate has not been explained, but a possible interpretation is that the addition of a carbonium ion to the dipolar *p*-nitrophenylacetic acid is facilitated by high ionic strengths (4).

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VITA

The author was born in Saskatoon, Saskatchewan, Canada, on November 12, 1924. She attended the Bishop Strachan School in Toronto, Canada, and graduated from that institution in 1942. In the fall of the same year she entered the University of Toronto from which she graduated with the B.A. degree in 1946. She was registered in the graduate college of the University of Illinois from 1946 until 1949, receiving the A.M. degree in 1947. She held university fellowships from 1946 to 1949.

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